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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/089,641	05/03/2002	Dae Gun Kim	6181/OK439	3102

7590 07/11/2005

S Peter Ludwig
Darby & Darby
Post Office Box 5257
New York, NY 10150-5257

EXAMINER	
WHITEMAN, BRIAN A	

ART UNIT	PAPER NUMBER
1635	

DATE MAILED: 07/11/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/089,641	KIM ET AL.	
	Examiner	Art Unit	
	Brian Whiteman	1635	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *2/22/05, 3/30/05*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *11-21* is/are pending in the application.

4a) Of the above claim(s) *11-18* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *19-21* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☒ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *1/28/05*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

S.O.D

DETAILED ACTION

Non-Final Rejection

Claims 11-21 are pending.

The amendment with the complete listing of the claims filed on 3/30/05 is acknowledged by the examiner.

Applicant's argument, the cancellation of claims 22-37 and the amendment to claim 19 in paper filed on 2/22/05 is acknowledged and considered by the examiner.

Election/Restrictions

Claims 11-18 remain withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a nonelected invention, there being no allowable generic or linking claim. Election was made **without** traverse in the reply filed on 10/5/04.

Information Disclosure Statement

The information disclosure statement (IDS) submitted on 1/28/05 was filed after the mailing date of the office action on 10/22/04. The submission is in compliance with the provisions of 37 CFR 1.97. Accordingly, the information disclosure statement is being considered by the examiner.

Oath/Declaration

The oath or declaration is defective. A new oath or declaration in compliance with 37 CFR 1.67(a) identifying this application by application number and filing date is required. See MPEP §§ 602.01 and 602.02.

The oath or declaration is defective because: the method claims 19-21 were not filed in the original application with the original oath and there is no statement or indication in the file of record that all of the inventors listed in the original oath were the inventors of the newly added method claims.

It is noted that Applicants indicate that they will provide a new oath upon allowance of claimed subject matter. Thus, the oath remains defective.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 19-21 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter, which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

> Factors to be considered in determining whether a disclosure would require undue experimentation have been summarized in In re Wands, 858 F.2d 731, 8USPQ2d 1400 (Fed. Cir. 1988). They include (1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims.

The claims read on using an expression vector comprising a genus of P972 gene to treat cancer in a mammal. The claims read on treating different types of cancer including cervical, breast, and colon cancer. Therefore, the claims are considered broad. The claims will therefore be evaluated based upon using an expression vector comprising a P972 gene to treat cancer in a mammal.

The test of enablement is whether one skilled in the art could make and use the claimed invention from the disclosures in the application coupled with information known in the art without undue experimentation (United States v. Telectronics, Inc., 8 USPQ2d 1217 (Fed. Cir. 1988). Whether undue experimentation is required is not based upon a single factor, but rather a conclusion reached by many factors. These factors were outlined in Ex parte Forman, 230 USPQ 546 (Bd. Pat. App. & Inter. 1986) and again in In Re Wands (see above).

At the time the application was filed, gene therapy was considered to be unpredictable due to significant problems in several areas. The state of the art, exemplified by Anderson et al., Nature, Vol. 392, pp. 25-30, 1998, displays major consideration for any gene transfer or any DNA therapy protocol involve issues that include:

1) The type of vector and amount of DNA constructs to be administered,

2) The route and time course of administration, the sites of administration, and successful uptake of the claimed DNA at the target site;

3) The trafficking of the genetic material within cellular organelles, the rate of degradation of the DNA, the level of mRNA produced, the stability of the mRNA product, the amount and stability of the protein produced, and

4) What amount of the expressed proteins considered to be therapeutically effective for a DNA therapy method.

In addition, all of these issues differ dramatically based on the specific vector used, the route of administration, the animal being treated, therapeutically effective amount of the DNA, and the disease being treated.

Anderson teaches that gene therapy is a powerful new technology that still requires several years before it will make a noticeable impact on the treatment of disease, and that several major deficiencies still exist including poor delivery systems, both viral and non-viral, and poor gene expression after genes are delivered (pp. 25-30).

Anderson further teaches that the reason for the low efficiency of gene transfer and expression in human patients is that we still lack the basis understanding of how vectors should be constructed what regulatory sequences are appropriated for which cell types (page 30, column 1, last paragraph). Furthermore, Verma, *Nature*, Vol. 389, pages 239-242, 1997, indicates that factors including the nature of the diseases and/or disorders, the nature of a DNA and/or target tissue, and a delivery system and/or amounts of the DNA complexes employed in the delivery system that would generate a therapeutic effect *in vivo* must be considered for any gene therapy method to be successful (page 238, columns 1 and 2).

In further view of the doubts expressed above by Anderson and Verma, the state of the art for cancer gene therapy as discussed by Vile et al., (Gene Therapy, Vol. 7, pp. 2-8, 2000). Vile teaches:

> The problems which gene therapy for cancer will take into the next millennium focus far less on the choice of therapeutic gene(s) to be used than on the means of delivering them. There is already a battery of genes that we know are very effective in killing cells, if they can be expressed at the right site and at appropriate levels. None the less, until the

> perfect vector is developed, the choice of gene will remain crucially important in order to compensate for the deficiencies of the vectors we currently have available (page 2, 1st paragraph, left column). Whatever its mechanism, no single genes can be a serious contender unless it has a demonstrable bystander effect (page 2, right column). The requirement for such a bystander effect stems directly from the poor delivery efficiency provided by current vectors (page 2, right column).
>
> A genuine ability to target delivery systems to tumor cells distributed widely throughout the body of a patient would simultaneously increase real titers and efficacy. In truth, no such systemically targeted vectors exist yet. Injection of vectors into the bloodstream for the treatment of cancer requires not only that the vectors be targeted (to infect only tumor cells) but also that they by protected (from degradation, sequestration or immune attack) for long periods of time so that they can reach the appropriate sites for infection. Moreover, having reached such sites, the vectors must be able to penetrate into the tumor from the bloodstream before carrying out their targeted infection (page 4, bottom left column and top right column).

Thus, at the time the application was filed, the state of the art for gene therapy was considered highly unpredictable.

For additional reviews of the unpredictability of the gene therapy art, see Gomez-Navarro et al., European Journal of Cancer, Vol. 35, pp. 867-885, 1999; McNeish et al., Gene Therapy, pp. 1-7, 2004; Green et al., Cancer Gene Therapy, 9:1036-1042, 2002; Alemany et al., Nature Biotechnology, 18:723-727, 2000; Gromeier, ASM News, 68:438-445, 2002. All references cited on a previous PTO-892.

With respect to claims 19-21 reading on an in vivo treatment method, the instant specification is only enabled for cancer therapy comprising directly administering to tumor cells lacking P972 expression said recombinant adenovirus comprising P972 gene and a promoter operably linked to the P972 gene and not for the full breadth of the claimed method because it would have taken one skilled in the art an undue and excessive amount of experimentation to practice using an expression vector in a genus of cancer cells (expressing or not expressing P972). The art of record teaches that cancer gene therapy is unpredictable. The unpredictability

taught by the art of record involves different types of cancer are affected differently or require DNA damage to see an affect. See McNeish (supra) and Gomez-Navarro (supra). The applicants teach that recombinant adenovirus coding for P972 can kill tumor cells lacking P972 expression in vitro (page 9); however, the art of record and the instant specification do not teach one skilled in the art how to correlate between results obtained in vitro studies set forth in the specification with results which the skilled artisan would reasonably expect to see in vivo in a genus of cancer cells. Furthermore, oncolysis in a cell line does not provide a nexus to treatment of tumors in vivo because the art of record and the instant specification do not provide sufficient guidance and/or factual evidence that killing tumor cells in vitro reasonably extrapolates to treatment of a tumor in vivo because killing tumor cells in vitro does not indicate that the number of tumor cells killed in a tumor in vivo is more than the number of new tumor cells in the tumor.

With respect to claim 20 reading on an in vivo method of treating cancer cells in a mammal, the instant specification is enabled for the directly delivering the adenovirus to cancer cells lacking P72 expression and not for using a genus of administration routes to treat cancer cells in a mammal because it would have taken one skilled in the art an undue and excessive amount of experimentation to practice using a recombinant adenovirus in a genus of administration routes. The applicants teach that recombinant adenovirus coding for P972 can kill tumor cells lacking P972 expression in vitro (page 9); however, the art of record and the instant specification do not teach one skilled in the art how to correlate between results obtained in vitro studies set forth in the specification with results which the skilled artisan would reasonably expect to see in vivo using a genus of administration routes. The art of record teaches that cancer gene therapy is unpredictable. The unpredictability taught by the art of record involves

poor and inefficient delivery of adenovirus to target a tumor, host immune response which limit the ability of the adenovirus to infect a tumor, failure to efficiently infect certain tumors which lack adenoviral receptor CAR, promiscuous tropism which causes uncontrolled adenoviral infection and gene transfer into normal bystander cells, uptake intake into the liver of adenovirus instead of uptake into target tumor when the virus is systemically (e.g., intravenous administration) delivered to a patient.

With respect to the term "p972 gene" in the instant claims, the specification defines the term as "the P972 gene modified to express the protein expressed by the wild type P972 gene or other proteins that functionally equivalent to the same as well as the wild type P972 gene (GenBank Accession No. AF078078 (page 5)." The instant specification also indicates that P972 is also referred to as Gadd45gamma, CR6, or OIG37 (abstract). Thus, the term is considered broad. The accession no. AF078078 in the instant specification is for GADD45gamma mRNA. The skilled artisan understands that sequences present in GenBank records can change from time to time and such changes are not defined by the disclosure or under control of the applicants. Furthermore, a search of the term in GenBank results in one hit for a Phytophthora alni subsp. (multiformis strain P972 internal transcribed spacer 1, partial sequence; 5.8S ribosomal RNA gene, complete sequence; and internal transcribed spacer 2, partial sequence) with a different GenBank Accession No. AY689136). In view of the diverse sequences that are embraced by the term, the skilled artisan could not use the genus of P972 genes in the claimed method without performing undue experimentation for determining which sequences are functionally equivalent to the wild type P972 gene (AF078078) in treating cancer cells lacking P972 expression.

The court in Enzo 188 F.3d at 1374, 52 USPQ2d at 1138 states:

It is well settled that patent applications are not required to disclose every species encompassed by their claims, even in an unpredictable art. However, there must be sufficient disclosure, either through illustrative examples or terminology, to teach those of ordinary skill how to make and use the invention as broadly as it is claimed.
In re Vaeck, 947 F.2d 48, 496 & n.23. 30 USPQ2d 1438, 1445 &n23 (Fed. Cir. 1991)(citation omitted). Here, however, the teachings set forth in the specification provide no more than a "plan" or "invitation" for those of skill in the art to experiment...; they do not provide sufficient guidance or specificity as to how to execute that plan. See Fiers v. Revel. 984 F.2d.1164, 1171, 25 USPQ2d 1601, 1606 (Fed. Cir. 1993); In re Wright, 999 F.2d...[1557], 1562, 27 USPQ2d...[1510], 1514. [Footnote omitted].

On this record, it is apparent that the instant specification provides no more than a plan or invitation in view of the art of record exemplifying the unpredictability of using a genus of P972 genes in the cancer gene therapy, for those skilled in the art to further experiment with a genus of sequences so as to provide a sufficient number of sequences that could be used in the claimed method of gene therapy as intended by the instant specification at the time the invention was made.

See also Genentech Inc. v. Novo Nordisk A/S, 108 F.3d 1361, 1366, 42, USPQ2d 1001, 1005 (Fed. Cir. 1997)

> ("Tossing out the mere germ of an idea does not constitute enabling disclosure. While every aspect of a generic claim certainly need not have been carried out by an inventor, or exemplified in the specification, reasonable detail must be provided in order to enable the public to understand and carry out the invention.")

In view of the art of record and the lack of guidance provided by the specification; the specification does not provide reasonable detail for what sequences are considered the functional equivalent of the wild type P972 gene, and it would take one skilled in the art an undue amount of experimentation to reasonably extrapolate from the assertion in the specification to practicing

the claimed invention. Therefore, the instant specification is not enabled for the claimed invention.

Given the above analysis of the factors, it is concluded that the instant specification and the claims coupled with the art of record, at the time the invention was made, the specification does not provide sufficient guidance and/or evidence to reasonable enable the claimed invention. Given that cancer gene therapy wherein an expression vector (adenovirus) is employed to treat a genus of tumors in a mammal was unpredictable at the time the invention was made, and given the lack of sufficient guidance as to using a genus of P972 genes in a cancer gene therapy as cited in the claims, one skilled in the art would have to engage in a large quantity of undue experimentation in order to practice the claimed invention based on the applicants' disclosure and the unpredictability of cancer gene therapy

Furthermore, the invention consists of an adenovirus designated AdP972. Claim 20 specifically claims the adenovirus. Since the adenovirus is essential to the claimed invention, it must be obtainable be a repeatable method set forth in the specification or otherwise readily available to the public. If the adenovirus is not so obtainable or available, the requirements of 35 U.S.C. 112, regarding "how to make", may be satisfied by a deposit of the adenovirus. It does not appear that the adenovirus is known and readily available or can be reproducibly made without undue experimentation, and because claim 20 specifically requires the adenovirus. If a deposit is made under the terms of the Budapest Treaty, then an affidavit or declaration by Applicants, or a statement by an attorney of record over his or her

signature and registration number, stating that the instant invention will be irrevocably and without restriction released to the public upon the issuance of a patent, would satisfy the deposit requirement made herein. If a deposit has not been made under the Budapest Treaty, then in order to certify that the deposit meets the criteria set forth in 37 CFR 1.801-1.809 and MPEP 2402-2411.05, Applicant may provide assurance of compliance by affidavit or declaration, or by a statement by an attorney of record over his or her signature and registration number showing that:

(a) during the pendency of the application, access to the invention will be afforded to the Commissioner upon request;

(b) all restriction upon availability to the public will be irrevocably removed upon granting of the patent;

(c) the deposit will be maintained in a public depository for a period of 30 years, or 5 years after the last request of the enforceable life of the patent, whichever is longer;

(d) a test of the viability of the biological material at the time of deposit (see CFR 1.807); and

(e) the deposit will be replaced if it should ever become inviable.

This requirement if necessary when a deposit is made under the provisions of the Budapest Treaty as the Treaty leaves these specific matters to the discretion of each member State. Amendment of the specification to recite the date of the deposit and the complete name and address of the depository is required.

It is noted that page 17 of the instant specification is directed to a deposit of AdP972, however, this deposit is not considered a proper deposit under the terms of the Budapest Treaty.

Applicant's arguments filed 2/22/05 have been fully considered but they are not persuasive.

With respect to applicant argument that the specification provides in vivo data of tumor growth inhibition in nude mice for HM-7 tumor cells and the standard for patentability under 35 USC differs from the standard for regulatory approval by the Food and Drug Administration for marketing approval See Scott v. Finney 34 F3d 1058, 32 USPQ2s 115 (Fed. Cir. 1994) and In re Brana, 51 F3d 1560 (Fed. Cir. 1995), the argument is not found persuasive because the rejection of record does not address that the specification does not provide sufficient data to support a correlation between in vitro and in vivo efficacy and that the specification is not enabled for treating humans. The rejection was directed to using a genus of P972 genes in the claimed method and treating cancer cells that lack or do not lack P972 expression.

In addition, the applicants amended the claim 19 to recite direct administration of the adenovirus and deleted the claims directed to all Er-positive or metastatic tumors (claims 30-33). However, claim 20 still reads on using a genus of administration routes to treat cancer cells in a mammal and the applicants have not provided sufficient guidance and/or evidence to overcome the instant rejection of record.

Conclusion

The prior art made of record and not relied upon is considered pertinent to applicant's disclosure. The guidance in US 6,573,371 contemplates using SYG972 genomic DNA in cancer treatment. See column 10. The patent would be available for use in 103(a) because using SYG972 in cancer treatment would read on the claimed methods. See definition of p972 gene (page 5, lines 16-19). However, in view of the unpredictability in the art for using the claimed method, one of ordinary skill in the art would determine that there would be no reasonable expectation of success using SYG972 genomic DNA in cancer treatment or for determining if SYG972 is the functional equivalent of a P972 gene when treating cancer cells lacking P972 expression.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Brian Whiteman whose telephone number is (571) 272-0764. The examiner can normally be reached on Monday through Friday from 7:00 to 4:00 (Eastern Standard Time), with alternating Fridays off.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Andrew Wang, acting SPE – Art Unit 1635, can be reached at (571) 272-0811.

Papers related to this application may be submitted to Group 1600 by facsimile transmission. Papers should be faxed to Group 1600 via the PTO Fax Center located in Crystal Mall 1. The faxing of such papers must conform with the notice published in the Official Gazette, 1096 OG 30 (November 15, 1989). The CM1 Fax Center number is (703) 872-9306.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to (571) 272-0547.

Patent applicants with problems or questions regarding electronic images that can be viewed in the Patent Application Information Retrieval system (PAIR) can now contact the USPTO's Patent Electronic Business Center (Patent EBC) for assistance. Representatives are available to answer your questions daily from 6 am to midnight (EST). The toll free number is (866) 217-9197. When calling please have your application serial or patent number, the type of document you are having an image problem with, the number of pages and the specific nature of the problem. The Patent Electronic Business Center will notify applicants of the resolution of the problem within 5-7 business days. Applicants can also check PAIR to confirm that the problem has been corrected. The USPTO's Patent Electronic Business Center is a complete service center supporting all patent business on the Internet. The USPTO's PAIR system provides Internet-based access to patent application status and history information. It also enables applicants to view the scanned images of their own application file folder(s) as well as general patent information available to the public.

For all other customer support, please call the USPTO Call Center (UCC) at 800-786-9199.

Brian Whiteman
Patent Examiner, Group 1635